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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/068,293	05/06/98	SANDALON Z	AEM96-01A

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EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	9

DATE MAILED: 05/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/068,293	Applicant(s) Sandalon et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Feb 16, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-46* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-46* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Amendments to the specification in Paper No. 8, filed February 16, 2000 has overcome the some of the rejections of claims 1-46 under 35 USC 112, second paragraph in the previous office action, and those rejections are withdrawn, while sustained rejections are accompanied by responses to the arguments of Paper No. 8.

2. Arguments filed in Paper No. 8 regarding the rejection of claims 18, 19, 21, 24, 29 and 30 under 35 USC 102(b) over Forstova et al. have been fully considered and are persuasive. The rejection is withdrawn.

3. Amendments to the specification in Paper No. 8 have overcome the objection to the specification in the previous office action, and the rejection is withdrawn.

4. Amendments to the claims in Paper No. 8, have overcome the rejection of claims 1-17 under 35 USC 112, first paragraph, scope of enablement, in the previous office action, and the rejection is withdrawn.

5. Amendments to the claims in Paper No. 8, have overcome the objection of claims 1 and 18 in the previous office action, and the rejection is withdrawn.

6. Claims 7, 10, 12, 25, 28 and 32 have been amended to state "DNA which encodes a protein or peptide product wherein said protein or peptide product is not made or contained in said cell" in response to a rejection under 37 CFR 112, second paragraph. For the purposes of

examination, this language is interpreted to mean that the protein or peptide which is encoded by the DNA of the construct is not made or contained in the cell at any time, which time includes that time when the cell may contain the DNA construct.

Claim Objections

7. Claim 1 is objected to because of the following informalities: newly entered claim limitations duplicate existing claim language at lines 4, 7, 10 and 12. Appropriate correction is required.

8. Claim 6 is objected to because of the following informalities: newly entered claim limitations duplicate existing claim language at line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 41, 42 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* constructs, does not reasonably provide enablement for *in vivo* therapeutic use for the construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The claims are drawn to a construct of SV40 viruses or pseudoviruses comprising exogenous nucleic acid and at least one pure or semi-purified SV40 capsid protein wherein the exogenous nucleic acid or an exogenous protein is therapeutic and therapeutic methods of using the construct. While applicants have shown *in vitro* constructs, they have not demonstrated *in vivo* therapeutic use for the construct. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve experimentation with SV40 constructs *in vivo* to demonstrate therapeutic activity of the constructs.

b- Applicants have provided guidance and working examples of the constructs *in vitro* and no working examples and only limited prophetic guidance for therapeutic use of the constructs *in vivo*.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

11. ***Response to Arguments***

Arguments set forth in Paper No. 8 assert that the references provided with the response show that the claims are enabled. The references provided in the response of Paper No. 8 have publication dates after the priority filing date of the instant application, and may not be used as proof of enablement. Therefore the arguments are moot.

12. Claims 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to therapeutic methods of using the construct of SV40 viruses or pseudoviruses comprising exogenous nucleic acid and at least one pure or semi-purified SV40 capsid protein. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve experimentation with SV40 constructs *in vivo* to demonstrate therapeutic activity of the constructs.

b- Applicants have provided guidance and working examples of the constructs *in vitro* and no working examples and only limited prophetic guidance for therapeutic use of the constructs *in vivo*.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended

host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

13. ***Response to Arguments***

Arguments set forth in Paper No. 8 assert that the references provided with the response show that the claims are enabled. The references provided in the response of Paper No. 8 have

publication dates after the priority filing date of the instant application, and may not be used as proof of enablement. Therefore the arguments are moot.

14. Claims 1-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SV40 capsid formation using VP1 alone, does not reasonably provide enablement for SV40 capsid formation using VP2 or VP3 alone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Since the specification shows that the use of VP2 and VP3 without VP1 does not result in capsid formation, the claims and specification are not enabled for the claims as written. Either VP1 alone or VP1 in combination with VP2 and VP3 are the only enabled embodiments.

15. Claims 1-17 and 35-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not sufficiently describe the possible inventions drawn from the claims. There is no information given regarding the structures of a gene that may suggest potential antisense oligonucleotides which may be created or found. The mechanism of action of an antisense oligonucleotides requires specific knowledge of target nucleic acids or their

complements. The specification provides no disclosure as to which portions of the nucleic acids are structurally important; therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of any of these compounds at the time of filing of the instant application.

16. ***Response to Arguments***

Arguments set forth in Paper No. 8 assert that the prior art teachings are relied upon to provide description of any antisense molecule and its potential target. However, the prior art taught at the time of filing of the instant application, that an antisense molecule could not be predicted from a large tract of DNA (such as a gene) and that the only way to identify the active region of a large tract was by trial and error testing of each and every oligonucleotide in the entire tract until an active oligonucleotide was found. The lack of predictivity, makes the identification of an antisense molecule a trial and error process, which is contrary to the concept of enablement.

17. Claims 1-8, 10-26 and 28-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification at pages 19-20 makes clear the necessity of having an *ori* sequence in each nucleic acid which is encapsidated in the claimed SV40 protein capsid structures. Since claims 9 and 27 specifically recite that the DNA sequence comprises said *ori* sequence, this makes it clear that the claimed subject matter of claims 1-8, 10-26 and 28-46 are

therefore contemplated as **not** having an *ori* sequence, which as stated above is taught against by the instant specification.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 1-17, 20, 25 and 27-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Claim 1 recites the phrase "capable of" which renders the claim(s) indefinite because the capacity of a compound to perform some function is merely a latent characteristic of said compound and said language carries no patentable weight. See MPEP § 2173.05(b), (d) and (g).

21. ***Response to Arguments***

Arguments set forth in Paper No. 8 assert that because the construct has an intended use, that this justifies the use of the term "capable of" in the preamble of the claim. Intended use does not remove the uncertainty of the term "capable of".

22. Claim 1 recites the limitation "exogenous protein" in line 26. There is insufficient antecedent basis for this limitation in the claim.

23. Claim 1 is rejected because of an internal inconsistency. Section "e)" in the Markush Group states that the "constituent" is an "exogenous protein of peptide product". There is no

provision in this section for a DNA. Therefore, the "DNA construct" of the claim is left without a DNA element as the limitations of section "e)" are applied to the claimed "DNA construct".

24. Claim 1 is rejected because it recites that a "DNA construct" **comprises** (emphasis added) a protein. The term "DNA construct" is an art recognized term which does not allow for a protein to be a part of a DNA. Using the word "complex" would cure this defect.

25. Claim 1 recites in section "d)" "an exogenous RNA encoding an exogenous protein or peptide product or itself a protein or peptide product". Is the RNA meant to be a protein? The meaning of this phrase is not understood. Appropriate correction is required.

26. Claim 1 recites at line 18, "regulatory elements sufficient for one or more of the following: (i) replication of said constituent". An origin of replication is not an art recognized "regulatory element". Appropriate correction is required.

27. Claim 6 recites "exogenous circular or linear DNA encoding a protein product, or encoding RNA, or a vector comprising exogenous DNA encoding RNA or encoding an exogenous protein or peptide product". Is the "vector" part of the "encoding RNA"? Do all of the DNA, RNA and vector encode the protein or peptide product or is that a property of the circular or linear DNA? The language of the claim is unclear and leaves open to speculation what is being claimed. Appropriate correction is required.

28. The terms "abnormally low amount" or "normal amount" in claims 7, 10, 12, 25, 28 and 32 is a relative term which renders the claim indefinite. The terms "abnormally low amount" or "normal amount" are not defined by the claim, the specification does not provide a standard for

ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without proper guidance as to the metes and bounds of the claims, one of ordinary skill in the art would not know when the characteristics of the protein in question stopped being an "abnormally low amount" or "normal amount".

29. ***Response to Arguments***

Arguments are set forth in Paper No. 8 which assert that those of skill in the art can agree on the definition of the term "normal", giving the relative terms of the claims definition. It is precisely the point of the definition of the term "normal" which is at question. The use of the term "normal" is **NOT** defined as exemplified by the following: "I am not feeling normal today, but I always feel this way. Therefore, is this normal?" In addition, one of skill in the art would not know what is a "normal" amount especially when ranges are being discussed, since the boundaries or outlier values are evaluated only by some arbitrary limit, which is not defined except by the fact that it is arbitrary.

30. The term "defective form" in claims 7, 10, 12, 25, 28 and 32 is a relative term which renders the claim indefinite. The term "defective form" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without proper guidance as to the metes and bounds of the claims, one of ordinary skill in the art would not know when the characteristics of the protein in question stopped being a "defective form".

31. Claim 16 recites "liver cells" as being an independent entity, and then in claim 17 recites "liver cells" as being a subset of "hemopoietic cells". These claims are internally inconsistent. Appropriate correction is required.

32. Claim 20 recites the limitation "said nucleic acid" in line 4. There is insufficient antecedent basis for this limitation in the claim.

33. Claim 27 recites the limitation "said cell" in line 4. There is insufficient antecedent basis for this limitation in the claim.

34. Claim 30 recites the limitation "said cell" in line 2. There is insufficient antecedent basis for this limitation in the claim.

35. Claim 32 recites the limitation "said cell" in lines 3, 4 and 6. There is insufficient antecedent basis for this limitation in the claim.

36. Claim 33 recites the limitation "said cell" in line 1. There is insufficient antecedent basis for this limitation in the claim.

37. Claim 37 recites the limitation "exogenous nucleic acid" in line 4. There is insufficient antecedent basis for this limitation in the claim.

38. Claim 42 recites the limitation "human cell" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

39. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

40. Claims 1-7, 9, 10, 12, 16-25, 27-34, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Christensen et al (of record).

Christensen et al. taught (see especially the abstract, the introduction, the figures, pages 438-439 and the discussion) a method of construction of SV40 viruses and pseudoviruses comprising a semi-purified or pure SV40 capsid protein and at least one other SV40 protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses. The pseudoviruses were treated with nuclease to remove non-packaged DNA. The DNA was circular or linear.

41. ***Response to Arguments***

Arguments set forth in Paper No. 8 assert that Christensen et al. do not teach exogenous DNA. Christensen et al. taught at page 433, column 2, "assembly was attempted using an exogenous source of viral DNA, i.e., SV 40 nucleoprotein complex (White and Eason, 1971), and empty virion shells." Therefore, the DNA of Christensen et al. fulfills the limitations as set forth in the claims. Other arguments set forth relate to limitations which are not claimed, and as such, are not relevant to the issues of the rejection.

42. Claims 1-7, 9, 10, 12, 16-25, 27-34, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Colomar et al. (of record, "AS").

Colomar et al. taught (see especially the abstract, the introduction, materials and methods, the figures and the discussion) a method of construction of SV40 viruses and pseudoviruses comprising a semi-purified or pure SV40 capsid protein and at least one other SV40 protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses. The pseudoviruses were treated with nuclease to remove non-packaged DNA. The DNA was circular or linear.

Claim Rejections - 35 USC § 103

43. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

44. Claims 1-13, 15-37 and 39-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen et al. or Colomar et al. (above) each in view of Carswell et al. (of record), Oppenheim et al. (J. Virol. Vol. 66, 1992, of record) and US Pat No. 5,863,541.

Christensen et al. or Colomar et al. each taught the invention described above. Also claimed is that the exogenous nucleic acid may be RNA, or antisense, and/or may encode a

protein, receptor, structural protein, regulatory protein or hormone, which may be a therapeutic protein.

Christensen et al. or Colomar et al. did not teach the exogenous nucleic acid may be RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone, which may be a therapeutic protein

US Pat No. 5,863,541 taught (see especially the abstract, the summary, column 5 and the claims) the production of AAV capsid proteins which were allowed to self assemble into capsids and then the exogenous nucleic acid was added to give pseudoviruses. The exogenous nucleic acid may be DNA, RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone, which may be a therapeutic protein. The host cell may be a human cell.

Carswell et al. taught (see especially the abstract) the advantage of combining an SV40 agnoprotein with SV40 capsid proteins to facilitate the assembly of capsids.

Oppenheim et al. (see especially the abstract) taught the advantage of combining an SV40 ori sequence with SV40 capsid proteins to facilitate the assembly of capsids.

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of Christensen et al. or Colomar et al. with the method of US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because the capsids proteins of US Pat No. 5,863,541 were assembled in a like manner to the instant claimed invention, and inclusion of nucleic acids which encode various therapeutic

entities is an obvious extension of the gene therapy teachings of Christensen et al. or Colomar et al. and because the AAV capsids of US Pat No. 5,863,541 were used for the same purpose and demonstrated the generally accepted practice of making pseudovirions for delivery of exogenous nucleic acids and proteins to cells. It is assumed that the making of AAV pseudovirions and SV40 pseudovirions is equivalent for the purpose of delivering exogenous nucleic acids and proteins to cells. Carswell et al. and Oppenheim et al. merely taught well known and advantageous methods of facilitating the assembly of SV40 capsid proteins into SV40 capsids.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the method of Christensen et al. or Colomar et al. with the method of US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because US Pat No. 5,863,541 recited at column 3, lines 11-13, "[m]olecules which may be associated with or encapsidated into capsids include DNA, RNA, proteins, peptides, small organic molecules, or combinations of the same.", continuing at lines 26-27, "[t]his system may be particularly advantageous in AAV gene delivery systems...". Then at column 4, lines 21-23, "[m]ethods for the *in vitro* construction of AAV capsids and for the *in vitro* packaging of these capsids are also provided." Colomar et al. recite at page 2785, column 2 "[t]hese experiments show that it is possible to reconstitute *in vitro* infectious virus-like particles". Therefore, the capsids of US Pat No. 5,863,541 and Christensen et al. or Colomar et al. were intended for the same purpose, where US Pat No. 5,863,541 utilized AAV capsids and Christensen et al. or Colomar et al. utilized SV40 capsids. Carswell et al. and Oppenheim et al. merely taught well

known and advantageous methods of facilitating the assembly of SV40 capsid proteins into SV40 capsids. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Christensen et al. or Colomar et al. with Carswell et al., Oppenheim et al. and US Pat No. 5,863,541.

45. ***Response to Arguments***

Arguments set forth in Paper No. 8 assert that the AAV capsids of US Pat No. 5,863,541 are different from the instant SV40 capsids, and the comparison is invalid. US Pat No. 5,863,541 is relied upon here to show a well known use of capsid proteins to encapsidate foreign nucleic acids including antisense.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the references are justifiably combined since each of US Pat No. 5,863,541, Carswell

et al. and Oppenheim et al. was used to demonstrate well known and obvious elements which are used to study related subject matter as the instant SV40 virion encapsidation.

46. Claims 14 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen et al. or Colomar et al. each with Carswell et al., Oppenheim et al. and US Pat No. 5,863,541. as applied to claims 1-13, 15-37 and 39-46 above, and further in view of Szczylik et al. (of record).

The claims are rejected for all the reasons above and because Szczylik et al. taught (see especially the abstract, materials and methods and the figures) an antisense oligonucleotide to *bcr/abl*.

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. and US Pat No. 5,863,541 with the antisense oligonucleotide of Szczylik et al. to produce the instant invention because Forstova et al. or Christensen et al. with US Pat No. 5,863,541 taught the inclusion of antisense oligonucleotides in the assembled SV40 pseudocapsids. The antisense oligonucleotide of Szczylik et al. being an obvious choice of one of the many antisense oligonucleotides within the purview of one of ordinary skill in the art at the time of the instant invention.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. and US Pat No. 5,863,541 with the antisense oligonucleotide of Szczylik et al. to produce the instant invention

because the antisense oligonucleotide of Szczylik et al. was an obvious choice of one of the many antisense oligonucleotides within the purview of one of ordinary skill in the art at the time of the instant invention. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Forstova et al. or Christensen et al. with US Pat No. 5,863,541 and with Szczylik et al.

Conclusion

47. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
May 3, 2000

ROBERT A. SCHWARTZMAN
PATENT EXAMINER